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November 1961

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CONTENTS

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1. Newsome, C. K.: The challenge of triacetyloleandomycin in pediatric infections, J. Indiana M.A., *53*:1131 (June) 1960.

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References:

1. Council on Foods and Nutrition. Vitamin Preparations as Dietary Supplements and as Therapeutic Agents. J.A.M.A. 169:110 (Jan. 3) 1959.
2. May, C. D.: Editorial. Pediatrics 23:833 (May) 1959.
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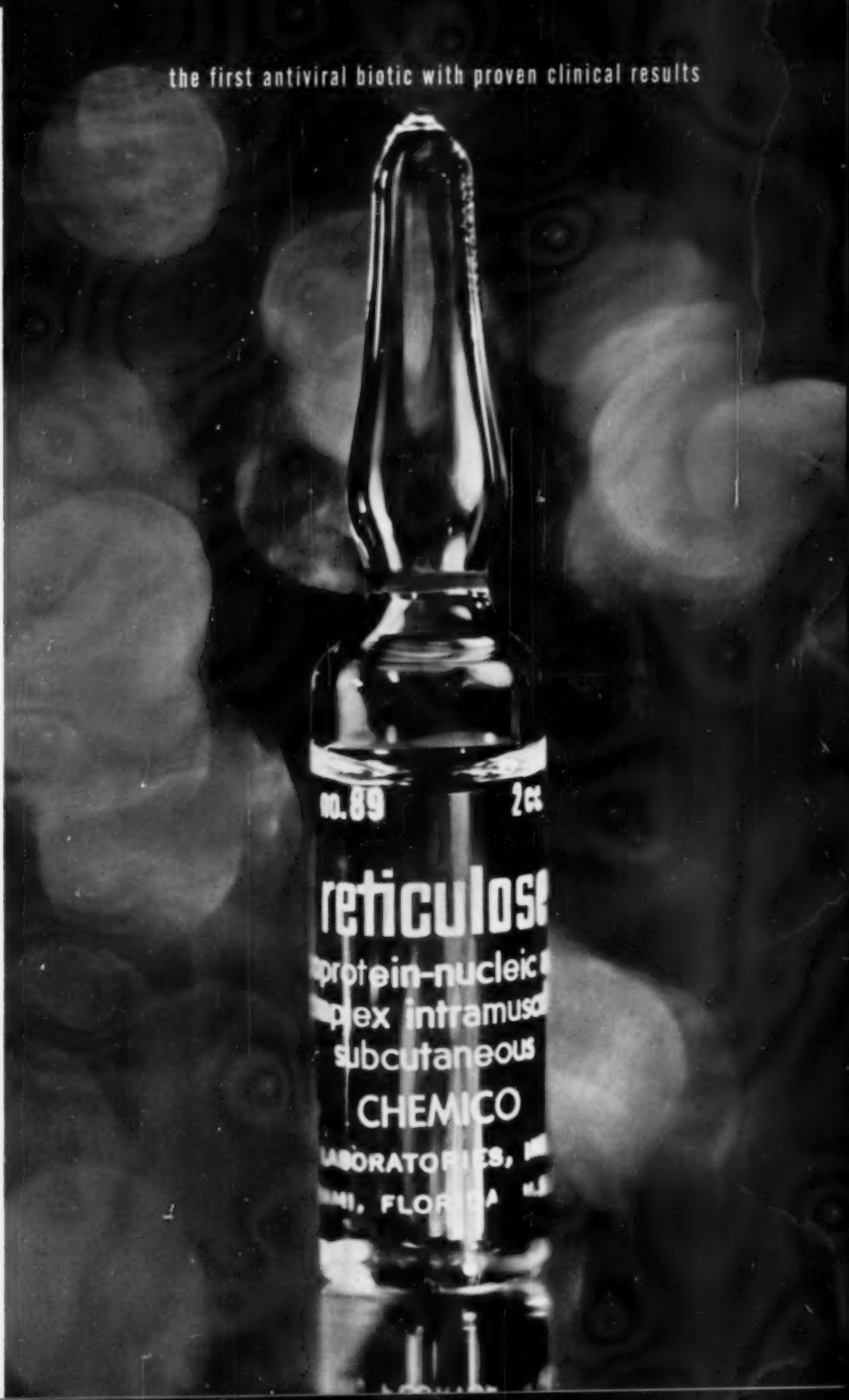
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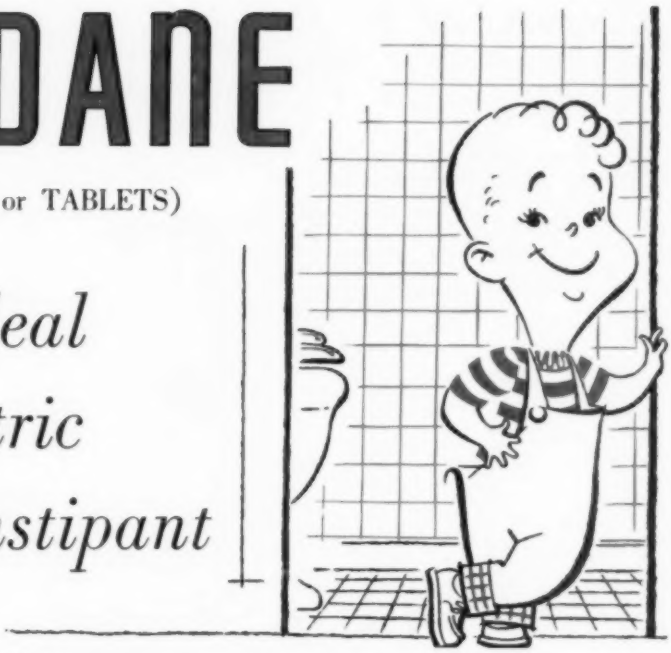

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1. Budetti, J. A., and Seydell, E. M.: *J. Kansas M. Soc.* 57:59, Feb., 1956. 2. Soss, T. L., in Collect. Letters, Internat. Cor. Soc., Ophthalmologists & Otolaryngologists 3:177, Dec. 15, 1958.

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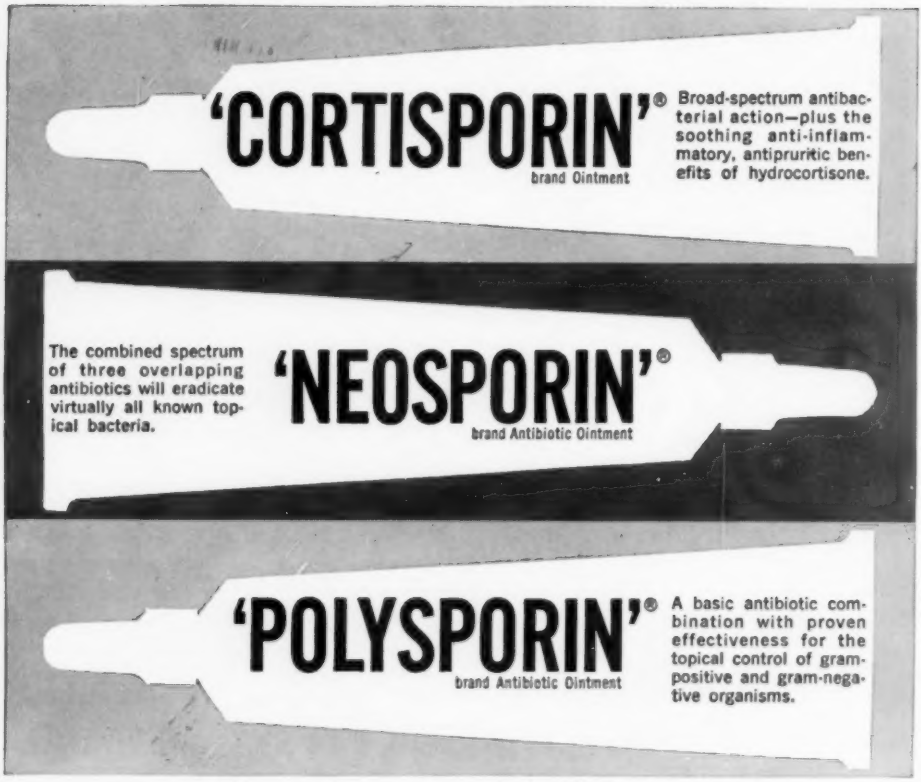

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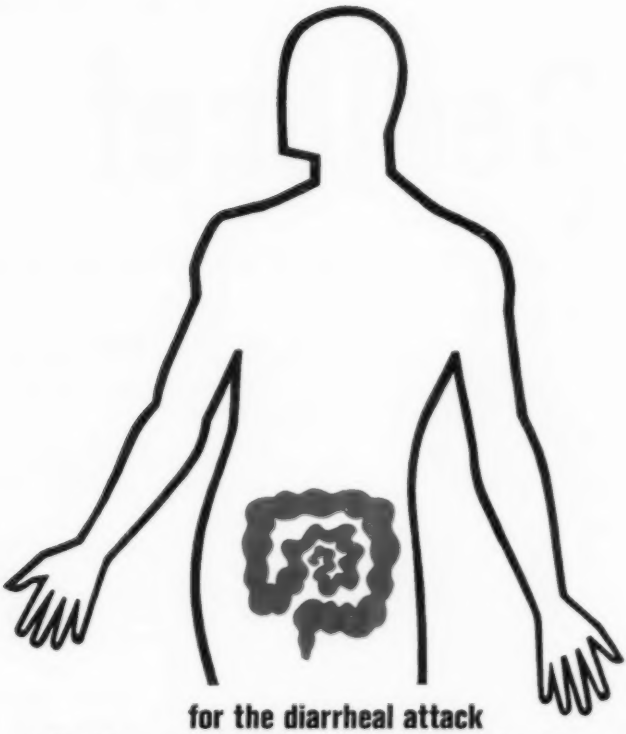

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1. Mintz, A. A.: Antibiot. Med. 7:481, 1960.

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Nandrolone-Phenpropionate in Progressive Muscular Dystrophy

A PRELIMINARY REPORT

I. A. Brown, M.D., Ph.D.*
E. M. James, M.D.**
Minnesota

The clinical features of progressive muscular dystrophy are those of unrelenting weakness, atrophy of the muscles and a genetic history. The latter is not always present nor is the distribution of the muscle involvement the same in all individuals. This feature has given rise to much clinical confusion as several variants have been described largely dependent upon the area of muscular involvement. Myotonia dystrophica for example, a disease with muscle weakness, testicular atrophy, alopecia and cataracts is now considered to be a form of progressive muscular dystrophy. Biochemical studies have demonstrated some changes which must be added to the clinical definition of the disease. These are: an increase in urinary creatine output, a decreased tolerance to exogenous creatine, a decrease in muscle phosphocreatine and an increase in the serum aldolase and transaminase (S.G.O.T. and S.G.P.T.). The assessment of any therapeutic agent is most difficult on clinical grounds alone and one can only judge its efficacy on whether or not it causes a decrease in the creatinuria.

At the present time no cure exists for progressive muscular dystrophy. This lamentable fact is due to the lack of knowledge about its pathogenesis. As a consequence a variety of therapeutic agents have been tried, including Vitamin C, Vitamin E (alpha-tocopherol), ATP (Adenosine-triphosphate), liver and pancreatic extracts and amino acids with little success. In recent years attention has been focused upon the hormones and some measure of success claimed. The virilizing side effects of earlier hormonal preparations have been reduced while at the same time greater anabolic effects have been attained. Noran-drostenolone-phenylpropionate synthesized in 1957 exhibited low-virilizing, high-anabolic activity and its use in progressive muscular dystrophy was reported by deToni in 1959.[1] In his study of this drug deToni noted a gain in weight, increased muscular strength and a reduction of the creatinuria in progressive muscular dystrophy. Bekeny, Kraft and Lang[2] studied methylandrostenediol on thirty patients with progressive muscular

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dystrophy. Of the group, five showed considerable improvement and the best results were observed in the pelvi-femoral type of progressive muscular dystrophy. There was negligible masculinization. In the report of deToni[1] the creatinuria disappeared in one of the three cases studied and this was accompanied by clinical improvement. Although inconclusive, the results of deToni indicate a need for further study. This report is in pursuance of that need.

A fourfold approach was planned to determine whether or not the drug nandrolone phenpropionate (Durabolin)* was therapeutically useful in progressive muscular dystrophy. A clinical, biochemical and electromyographic evaluation was done in addition to a study of the muscle biopsy. Baseline values were determined prior to institution of the drug and all studies were repeated three months later. The drug was administered by school nurses, by the Visiting Nurses Association and in hospital Out-Patient Clinics. To those sixteen years of age or less, twenty-five milligrams were given intramuscularly once a week while fifty milligrams were given weekly to the adults.

The biochemical studies included urinary creatine and creatinine concentrations, serum aldolase and serum creatinine determinations. Muscle biopsies were performed initially and repeated as far as possible in the same muscle three months later. In addition to the H & E (hematoxylin and eosin) stains for microscopic study, phosphocreatine determinations were made on the tissue.

It is to be emphasized that this is a preliminary report as three months is an insufficient period for a proper evaluation of any therapeutic agent in this disease.

CASE MATERIAL

Eighteen patients were chosen at randon from a list of individuals provided by the local chapter of Progressive Muscular Dystrophy Society. The ages ranged from nine to fifty-nine and the male-female ratio was sixteen to two. The majority of patients were enrolled in the local Progressive Muscular Dystrophy Clinic and had been afflicted for several years. The diagnosis was in doubt in one patient on clinical grounds and one patient was considered to have myositis (Case No. 16, A. H.). Of those with progressive muscular dystrophy, nine had the pseudo-hypertrophic variety. One patient had the facio-scapulo-humeral variety (Landouzy-Dejerine) of progressive muscular dystrophy. One patient was considered to have the Charcot-Marie-Tooth form of progressive muscular atrophy (Case No. 6, D. Z.). This data is listed in Table I.

* Supplied by Organon, Inc., New Jersey.

TABLE I

CASE	AGE	DIAGNOSIS
1. S. T.	12	Pseudohypertrophic Muscular Dystrophy
2. G. H.	19	Pseudohypertrophic Muscular Dystrophy
3. S. L.	18	Progressive Muscular Dystrophy
4. S. W.	15	Pseudohypertrophic Muscular Dystrophy
5. R. A.	33	Facio-Scapulo-Humeral
6. D. Z.	9	Charcot-Marie-Tooth
7. H. E.	12	Progressive Muscular Dystrophy
8. D. C.	22	Pseudohypertrophic Muscular Dystrophy
9. C. H.	37	Progressive Muscular Dystrophy
10. D. G.	9	Myotonia Congenita
11. J. K.	33	Progressive Muscular Dystrophy
12. R. C.	14	Progressive Muscular Dystrophy
13. M. H.	11	Pseudohypertrophic Muscular Dystrophy
14. J. M.	11	Pseudohypertrophic Muscular Dystrophy
15. S. D.	9	Pseudohypertrophic Muscular Dystrophy
16. A. H.	59	Polymyositis
17. K. P.	14	Pseudohypertrophic Muscular Dystrophy
18. S. F.	11	Pseudohypertrophic Muscular Dystrophy

CLINICAL EVALUATION

Table II summarizes the results of the administration of Durabolin to eighteen patients most of whom had progressive muscular dystrophy. Any clinical evaluation exhibits some bias—intended or not. Many difficulties are encountered in evaluating such diseases as progressive muscular dystrophy because of the prolonged course, severity and distribution of the weakness and atrophy and similarity to other myopathies. The clinical evaluation in this study was partly derived from responses by the mother or father whose judgment regarding drugs is usually not an objective one. A contrary opinion to this has been held by those who feel that the parents in their close contact with their afflicted offspring are reasonably good judges of slight differences. Be this as it may, very little stock is taken of any clinical evaluation in progressive muscular dystrophy because of the inherent difficulties of a subjective clinical evaluation.

The clinical examinations were done by qualified neurologists and consisted of the usual neurological examination plus detailed muscle testing and measurements of the extremities.

Of the eighteen patients (Table II) only two were considered to have improvements based on objective clinical grounds and these were regarded as *slight*. Sixteen, or eighty-eight per cent, experienced no objective improvement as based on clinical findings. Subjective improvement was experienced by six patients while twelve

TABLE II

CASE	SERUM ALDOLASE	URINE CREATINE	URINE CREATININE	SERUM CREATININE
1. S. T.	64	931	1274	1.3
2. G. H.	55	1175	1539	1.2
3. S. L.	49	140	2184	1.8
4. S. W.	23	314	405*	1.6
5. R. A.	95	1011	2080	1.4
6. D. Z.	13	347	1023	1.4
7. H. E.	48	501	697	1.2
8. D. C.	13	584	1238	1.8
9. C. H.	16	351	1813	1.7
10. D. G.	18	405	1478	1.5
11. J. K.	20	157	1386	1.7
12. R. C.		1554	2035	1.7
13. M. H.	90	665	1330	1.1
14. J. M.	83	715	975	1.2
15. S. D.	11	556	1145	1.3
16. A. H.	18	990	1500	1.4
17. K. P.	28	507	1410	1.4
18. S. F.	93	703	756	1.3

* Random specimen - not 24 hours.

TABLE III

P. M. D. PROJECT LAB DATA
RE-EVALUATION - THREE MONTHS

CASE	AGE	SERUM ALDOLASE	URINE CREATINE	URINE CREATININE	SERUM CREATININE
1. S. T.	12	51	658	901	1.2
2. G. H.	19	7	621	1024	1.4
3. S. L.	18	39			1.6
4. S. W.	15	23	1215	2115	1.2
5. R. A.	33	80	737	1843	1.3
6. D. Z.	9	8	301	893	1.0
7. H. E.	12	31	442	885	1.2
8. D. C.	22	12	662	1280	1.4
9. C. H.	37	24	1128	3416	1.7
10. D. G.	9		58	899	1.4
11. J. K.	33	20	85	127	1.9
12. R. C.	14	12	87	1344	1.2
13. M. H.	11	58	288	903	1.0
14. J. M.	11	53	354	483	1.1
15. S. D.	9	5	37	122	1.4
16. A. H.	59	14	35	519	1.7
17. K. P.	14	21	597	1311	1.2
18. S. F.	11	84	748	1101	1.2

noted no change. The parents of six of the patients felt that there was some generalized improvement. Seven of the patients noted a gain in weight. Fifteen of sixteen individuals with accurate measurements showed an increase in the size of the extremities.

LABORATORY EVALUATION

The clinical definition of progressive muscular dystrophy has been expanded to include an increase in urinary creatine excretion and an increase in serum aldolase. Despite this acquisition very

little has been added to the pathogenesis of the disease, since creatinuria has been encountered in other conditions with loss of muscle substance. No specificity, therefore, can be attached to this biochemical change at this moment. This non-specific response is considered to be the result of the failure of diseased muscles to metabolize creatine with its consequent excretion in the urine.

The concentration of these substances was determined in this case material before and after treatment and the values summarized in Table III.

The normal urinary creatine and creatinine excretion values for this laboratory were 0-250 milligrams per twenty-four hours and 0-125 milligrams per twenty-four hours respectively.** A glance at this table shows elevated values in all but one case. Elevations were also determined for the serum creatinine in twelve cases, or sixty-six per cent.

TABLE IV

MUSCLE PHOSPHOCREATINE

CASE	MUSCLE	WEIGHT (mgm.)	PHOSPHOCREATINE (ug.)
1. S. T.	V. Medialis	160	73
	Gastroc.	160	144.9
2. G. H.	V. Medialis	170	84
	L. Gastroc.	75	0
3. S. L.	V. Quad.	110	95
	Deltoid	150	18.5
17. K. P.	R. Quad.	350	42.86
	R. Gastroc.	70	0
18. S. F.	R. Quad.	400	34.8
	R. Gastroc.	130	0

Table IV shows the creatine, creatinine excretion values and serum creatinine levels after three months on Durabolin. Fourteen patients, or eighty-two per cent, exhibited a decrease in urinary creatine while sixty-six per cent, or twelve patients, showed a decrease in the urinary creatinine excretion. Eleven patients, or sixty-four per cent, exhibited a decrease in serum creatinine levels. Of the nine patients with pseudohypertrophic muscular dystrophy, six patients, or sixty-six per cent, showed a reduced value after three months of Durabolin therapy.

The enzyme aldolase discovered by Meyerhof, Lohmann and Schuster[3] (1936) catalyzes the conversion of fructase into phospho-

** Creatine determinations by Jaffe Reaction. Serum creatinine determinations by Folin-Wu.

glycer-aldehyde. It is a protein more soluble in the cold and is inhibited by heavy metals, iodine and glucose.

In 1949, Sibley and Lehninger[4] noted that patients with progressive muscular dystrophy had elevated serum aldolase values.* This has now become an important part of the definition of progressive muscular dystrophy. Evans and Baker[5] in 1957 examined sixty-four patients with myopathy and correlated the serum aldolase with the clinical findings. They found that the serum aldolase was elevated in thirteen cases of pseudo-hypertrophic muscular dystrophy and to a lesser extent in other types of dystrophy. The hyperaldolasemia was considered to represent a loss of enzyme from degenerating or necrotic muscles. In any event a raised serum aldolase is found in primary muscle diseases. An excellent review of serum enzyme activity in muscular dystrophy is to be found in the paper by Thompson and Leyburn.[6].

The serum aldolase was elevated in ten patients or fifty-five per cent of the total and after therapy, the serum aldolase was reduced in eight or eighty per cent of those ten patients. Although the exact significance of aldolasemia in progressive muscular dystrophy remains obscure, its reduction in a significant number of cases provides a basis for further research.

ELECTROMYOGRAPHY

Little can be said for electromyography in progressive muscular dystrophy at this time. Lack of standard procedures precludes any comparisons with studies elsewhere. Refinements in technique may yet prove helpful. Since in progressive muscular dystrophy the muscle is a mixture of normal and abnormal fibers, the use of co-axial needle electrodes would not necessarily sample a representative area of diseased muscle only. The number of normal fibers in most cases of progressive muscular dystrophy is such that some movement is possible—albeit weak and inadequate. The needle may be in an area of relatively normal musculature and record normal potentials. Multiple needles inserted into the muscles would be helpful but objectionable to the patients and the amount of data recorded so great that analysis would be difficult.

In this study muscle potentials were studied before and after therapy with Durabolin using co-axial needle electrodes. The signals were amplified by the Grass Model III-D and displayed on a

* Serum aldolase determinations performed by Bio-Sciences Laboratory, California.

dual beam oscilloscope and photographed. No specific changes were observed after therapy with the technique used herein.

MUSCLE BIOPSY

Morphological Study: The mysteries that surround the biochemical and clinical features of progressive muscular dystrophy have not been clarified by morphological study of the muscle biopsy. Very limited information is to be gained by a study of conventionally stained paraffin sections. In recent years, stains have been devised to identify and quantitate specific chemicals especially those concerned with the enzyme systems.

The microscopic alterations of progressive muscular dystrophy are well known. The individual skeletal muscle fibers stain poorly, vary in size and shape and many appear edematous. Precipitation of protein with complete disruption of muscle pattern and loss of striations is a common finding. In addition, the muscle fibers are separated from their surrounding sarcolemmal sheaths. Under low magnification the invasion and replacement of muscle by fat cells and connective tissue is characteristic as is the variation in density of the eosin stain. It must be remembered that these changes may be intermixed with normal appearing muscle. As far as is known there are no serial studies of the distribution of such change in an entire dystrophic muscle. It is generally assumed that the small section of muscle removed at biopsy is representative of the state of the muscle. This may not be in the case. Figures 1A, 2A, 3A, 3B, 4A, 4B demonstrate these changes.

Microscopic study of muscles biopsied three months after ingestion of Durabolin showed startling changes. Attempts were made to biopsy the same muscle as in the initial study. In some cases this was successful while in others the patients objected. The muscle was prepared in the same manner and stained with hematoxylin and eosin. The most striking change was the loss of edema as manifest by the lack of separation of muscle fibers from their sarcolemmal sheaths and the foamy, granular appearance of the individual fibers. The fibers were more uniform in size and shape. In most cases striations could be seen and in some cases this was the most obvious alteration. Those areas in which muscle was replaced by fat and connective tissue showed little change. These changes indicate the potentiality for reversal of a diseased muscle to a more normal state. It can be argued that the alterations described here might be relatively "normal" areas within a diseased muscle since in some cases

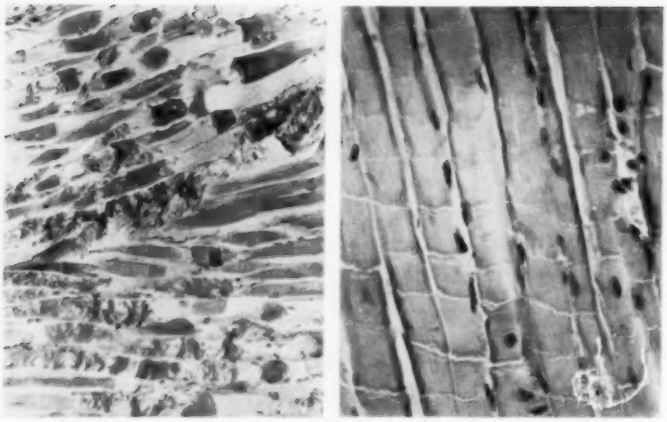


FIG. 1. A. Case No. 15. Low power section of muscle (deltoid) before therapy. Note extreme degree of fiber destruction as manifest by fragmentation, vacuolization and precipitation of muscle protein.

FIG. 1. B. Case No. 15. Same case three months after therapy. Section from same muscle as 1 A. More uniform appearance and striations readily observed.

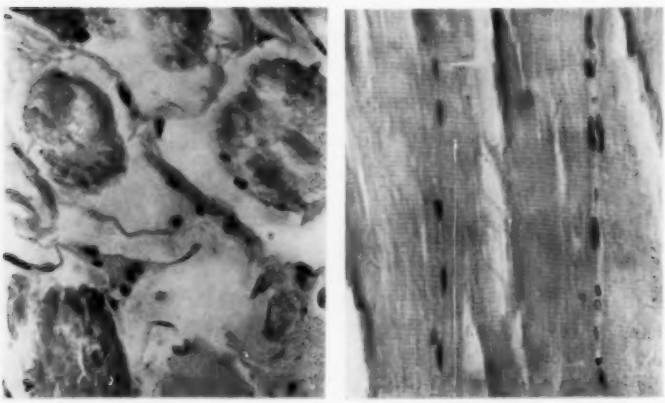


FIG. 2. A. Case No. 3. Biopsy before treatment showing changes in muscle fibers and separation of fibers from sarcolemmal sheaths. Longitudinal sections sometimes show muscle striations. 400 x

FIG. 2. B. Case No. 3. Biopsy three months after therapy showing striations, more normal appearing muscle. 400 x

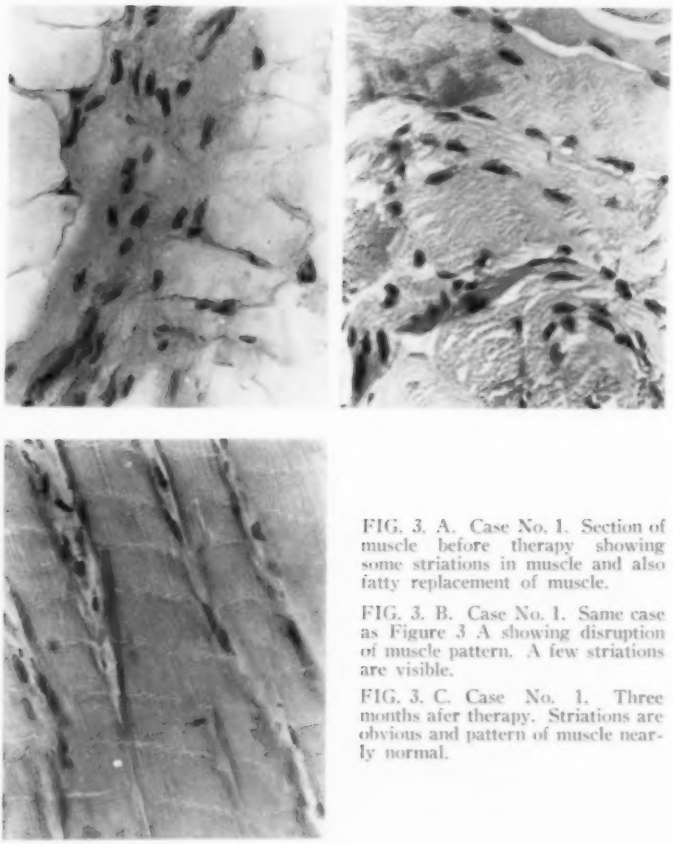


FIG. 3. A. Case No. 1. Section of muscle before therapy showing some striations in muscle and also fatty replacement of muscle.

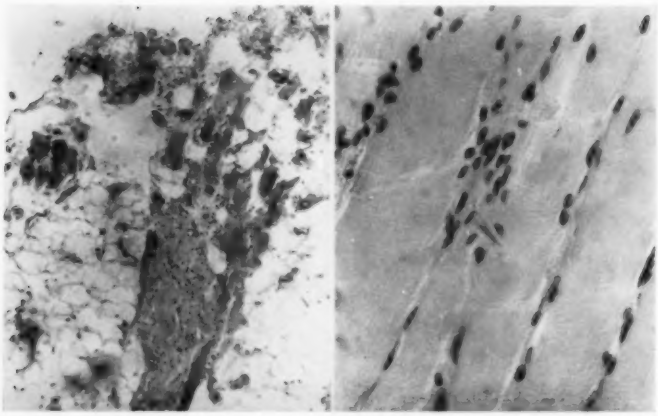
FIG. 3. B. Case No. 1. Same case as Figure 3 A showing disruption of muscle pattern. A few striations are visible.

FIG. 3. C. Case No. 1. Three months after therapy. Striations are obvious and pattern of muscle nearly normal.

the biopsies were taken from different muscles. The fact that these alterations occurred in all cases except those of polymyositis (Case No. 16) and the Charcot-Marie-Tooth form of progressive muscular atrophy (Case No. 6) negates the argument. Figures 1B, 2B, 3C, 4C, show changes after Durabolin therapy. These changes were present in eighty per cent of the cases.

Phosphocreatine Studies: In addition to the morphological study of the muscle, phosphocreatine determinations were made on the biopsied material.* Some difficulties were encountered in making a

* Technique of Bereblum and Chain as modified by Ennor and Stocken.



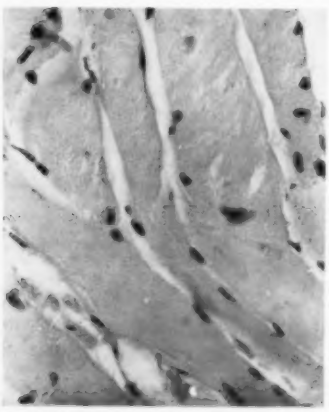


FIG. 4 A. and 4 B. Case No. 13. Sections showing variation in biopsy material. Replacement of muscle by fatty invasion and nearby area showing striations and more normal appearing muscle. 400 x

FIG. 4 C. Case No. 13. Muscle striations are apparent although some areas show disruption of muscle pattern. Three months after therapy. 400 x

complete survey of all cases because insufficient muscle was obtained for both phosphocreatine determinations and morphological study. Sufficient material was available in only five cases (1, 2, 3, 17, 18). The values are shown in Table IV. Of the five, a decrease in phosphocreatine was found in four cases, or eighty per cent. Most cases of progressive muscular dystrophy have had several muscle biopsies and are reluctant to have a large mass of muscle removed. They cannot be blamed for this attitude.

DISCUSSION

It is not possible on the basis of this study to make any sweeping

or dogmatic conclusions. The evidence for improvement is stronger in the laboratory and muscle evaluations than it is on clinical grounds. Two of the patients were strong in their claim for improvement. Most were not appreciably helped. This leads one to wonder just what criteria to accept as a measure of improvement. Quite obviously to the patient, it would be his ability to get around and out of his wheelchair. The study is a preliminary one and will be continued for a longer period of time. Three months is an insufficient time period for evaluation of any therapeutic agent in this group of diseases. In view of the preliminary nature of the study, the significance of the chemical changes is not discussed at this time. The chemical and morphological alterations, however, certainly point toward improvement and suggest the need for further study not only with this compound but also with other closely related substances.

SUMMARY

1. Eighteen patients were evaluated clinically, biochemically and morphologically before and after three months on Durabolin.

2. Six patients, or thirty per cent, noted improvement while only two, or twelve per cent, showed objective improvement.

3. Eighty-two per cent of the patients showed a dercease in urinary creatine and sixty-six per cent showed a decrease in urinary creatinine excretion.

4. Sixty-six per cent of the cases with pseudohypertrophic muscular dystrophy showed a decrease in urinary creatine excretion.

5. Eighty per cent of the cases (ten) that had elevated serum aldolase showed a decrease in the serum aldolase after three months on Durabolin.

6. Eighty per cent of the cases showed improvement in histological state of the muscles and eighty per cent showed a decrease in muscle phosphocreatine.

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Hepatic Changes in Kwashiorkor in Egyptian Children

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This paper is based on the findings obtained from 100 liver puncture biopsies taken from 30 cases of Kwashiorkor.

Thirty cases of Kwashiorkor were collected from the out-patient of Abbassia Children's Hospital during the period 1958-1960. They were admitted and treated in the in-patient department. Their ages ranged from 6 to 36 months. As a rule, these patients were brought to the hospital because of the edema.

In the present series of cases, the duration of the edema varied from one to six weeks and its onset was usually preceded by diarrhea, either of long or short duration. The extent of the edema varied. It was severe in 10 cases, moderate in 10, and mild in 10. The edema was considered severe when it was generalized; moderate when it involved the dorsae of the feet and hands, the legs and the face, and mild when it was limited to the dorsae of the feet and legs. A thorough clinical examination was carried out in all cases to exclude the presence of other organic diseases that may account for the edema, such as kidney or heart disease, or tuberculosis of the chest and abdomen.

Clinical examination of the abdomen revealed that the liver reached 3 fingers below the costal margin in 3 cases, and 2 fingers in 18 cases, while in the remaining 9 cases, it was not enlarged. When enlarged, the liver was rubbery in consistency with a smooth surface and a sharp edge.

The effect of treatment on the hepatic lesions present was studied. Mild cases were put on a high-protein low-salt diet, together with an ample supply of vitamins. Moderate and severe cases on the other hand were given, in addition, amino acids, liver extract, with or without plasma transfusions twice weekly.

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Liver puncture biopsy was performed in all cases on admission, and was repeated after subsidence of the edema, and once or twice more 2-4 weeks during convalescence. Further follow-up of these cases was not available.

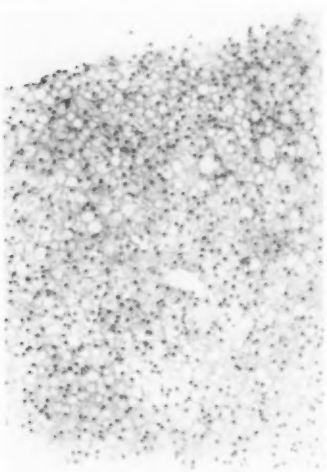

FIG. 1

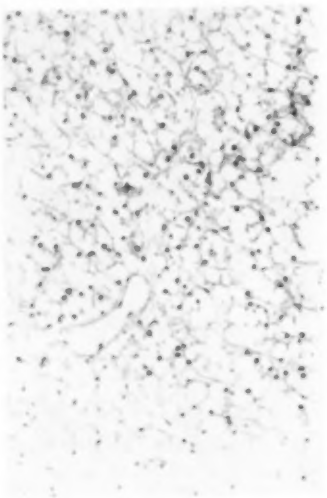

FIG. 2

RESULTS

From the histopathological study of these cases, it was apparent that the main feature was fatty infiltration of the liver cells. The degree of this fatty change varies from case to case depending on the severity of the condition and the duration of the illness. In moderate cases, it is to be seen principally toward the periphery of the lobules and sparing the liver cells around the central veins (Fig. 1). But in advanced and more severe cases, nearly all the liver cells are affected (Fig. 2). The amount of fat in the cells also varies. It usually appears as one globule which pushes the nucleus to one side. Sometimes the cells are ballooned by larger globules of fat so that they appear as micro cysts. The picture may be more severe with rupture of cell boundaries, loss of nuclear structures and actual necrosis of some of the liver cells. In cases where the disease has lasted for a few months, fibrosis around the portal tracts starts to be noticeable (Fig. 3). There is an increase of cellular fibrous tissue but there are no inflammatory cells or lymphocytic hyperplasia.

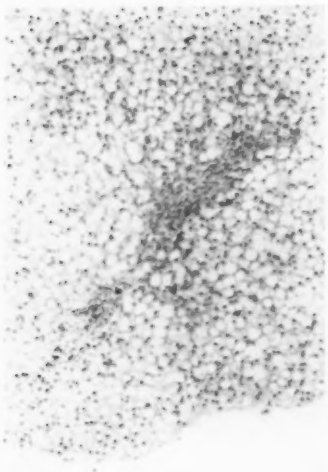

FIG. 3

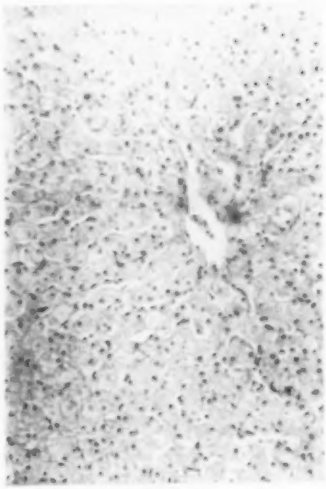

FIG. 4

By the time these changes take place, usually the fatty change becomes less marked and some of the liver cells show evidence of regeneration in the form of nuclear mitosis.

Early treatment may cause nearly complete disappearance of fat from the liver cells with restoration of the liver parenchyma to a ± normal picture (Fig. 4). The edema subsides first but the fatty change takes a much longer time to disappear. (See Case Reports) But if fibrosis has already started, this will persist. In more chronic cases, the portal fibrosis is more evident and the strands of fibrous tissue, which become less cellular, are seen to partially enclose nodules of liver tissue (Fig. 5).

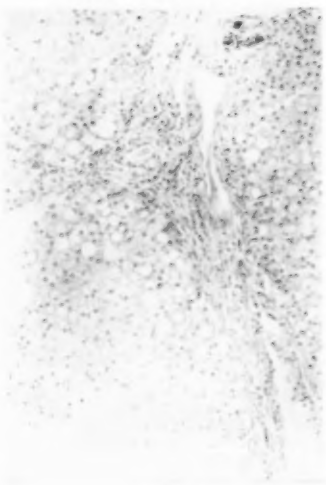

FIG. 5

It is to be noted, however, that in the cases examined, no marked alteration in the architecture of the liver or marked regenerative hyperplasia of liver cells was noticed. Therefore, although peri-

portal fibrosis is present, the cases so far followed up do not fulfill the pathological criteria needed for a diagnosis of liver cirrhosis. Further follow up of these cases is still necessary in order to tell whether or not some of them will end with genuine cirrhosis.

CASE REPORTS

The following case reports are cited here as illustrative examples of the 30 cases studied.

Case No. 1 A 30-month-old male patient, was admitted to the hospital with the complaint of generalized edema of two weeks' duration. This was preceded by diarrhea of 70 days' duration, following measles. On admission, the patient was 10.5 kgs. in weight and his liver was felt 3 fingers below the costal margin. Liver puncture biopsy showed the following:

1—Extensive fatty change involving the greater part of the lobules. In the lobules less affected, the change is chiefly in the peripheral and mid-zonal regions, while the central part shows evidence of albuminoid degeneration.

2—Slight condensation of the portal tracts. The patient was treated with protein milk, plasma transfusions, injections of amino acids, B_{12} and liver extract. After 10 days of treatment, the edema subsided completely, the body weight dropped by 2.2 kilos and the liver was only one finger below the costal margin. Liver puncture was then performed and it showed:

a—The fatty change is still present and fairly marked but less so than in the previous biopsy.

b—The fibroblastic proliferation of the portal tracts is more marked and is trying to enclose patches of liver tissue.

After another 10 days of treatment, a third biopsy showed:

1—The fatty change is still present but is now patchy, with no special distribution; is generally more marked toward the periphery of the lobules.

2—There is no significant change as compared with the second biopsy.

Case No. 2 A 24-month-old female patient (Fig. 6), who for 4-5 weeks had had edema of some severity, was admitted to the hospital.

She was weaned at 18 months, and since then suffered from chronic diarrhea, which became more severe during the last month, after an attack of measles.

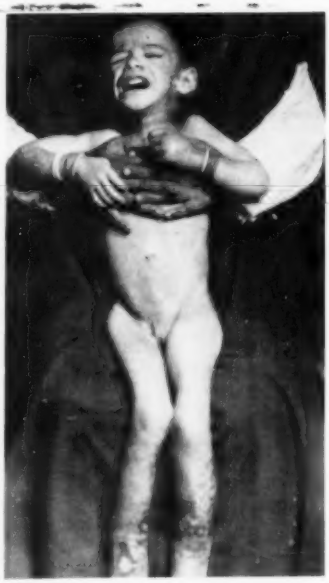

FIG. 6: Notice the apathetic look, the edema and the dermatosis.

On admission, the patient weighed 8 kgs. The liver was felt one finger below the costal margin and the liver puncture biopsy showed:

1—Moderate fatty change; in some parts diffuse and involving all lobules and in others more marked at the periphery.

2—Small foci of necrotic liver cells with hazy outline and absent nuclei.

3—In some areas the portal tracts are thickened by fibrous tissue.

4—Bordering the fatty cells in some areas there are hyperplastic liver cells which are smaller, and their nuclei show mitotic figures.

The patient was treated with protein milk together with injections of amino acids, B_{12} and liver extract. After 12 days of treatment, edema subsided and the body weight dropped by 1.2 kilos.

Liver puncture biopsy showed the following:

a—There is still evidence of mild fatty change and the liver cells are beginning to appear healthy.

b—The periportal fibroblastic proliferation is still present.

After another period of 3 weeks of treatment, the liver puncture showed the following:

1—A very mild fatty change in small groups of liver cells scattered here and there.

2—Some portal tracts are thickened and fibrotic.

Case No. 3 A 24-month-old male patient came to the hospital with severe edema of about 6 weeks' duration. Before that he had

severe diarrhea which lasted for 2 weeks only and ended with the onset of the edema. On admission, the patient weighed 8.5 kgs. The liver was felt 1.5 fingers below the costal margin and the liver puncture biopsy revealed:

1—Advanced fatty change in most of the liver lobules.
2—Small groups of liver cells showing necrosis.
3—Marked proliferation of fibroblasts in some of the small portal tracts.

The patient was put on a high protein diet and was given repeated plasma transfusions together with injections of liver extract, B_{12} and amino acids. Edema subsided within 8 days, the body weight dropped by 0.95 kilo and then liver puncture biopsy showed:

1—There is still fatty change but it is now of a mild degree.
2—Persistence of fibroblastic proliferation of the small portal tracts.

Treatment was continued for 2 more weeks. Liver puncture was then repeated and it showed:

1—The fatty change has almost disappeared.
2—The fibroblastic proliferation has not significantly changed.

Case No. 4 An 18-month-old female patient was admitted to the hospital with edema of moderate severity, of one week's duration. The patient was weaned 3 months previously and was put on a diet composed mainly of carbohydrates. Two months later she developed a severe diarrhea which lasted one week only; but since then, fearing recurrence, she was kept on simple infusions of karawya and anisi and on rice water, until she developed the present edema. On admission the patient weighed 7.5 kilos. The liver was felt 2 fingers below the costal margin and the liver puncture biopsy showed:

1—Extensive fatty change involving most of the cells in the lobules. In the lobules less affected, the change is more marked in the peripheral and midzonal portions.
2—Some liver cells show necrosis with granules of bile pigment.
3—No evidence of fibroblastic proliferation.

The patient was treated with a high protein diet only. After 6 days' treatment, her weight dropped by 0.75 kilos and the edema subsided. Liver puncture biopsy then showed that the fatty change had greatly been reduced. Treatment was continued for another 10 days. Liver puncture was repeated and it showed that the fatty change had almost disappeared, without any evidence of fibrosis of portal tracts.

DISCUSSION

The pathological findings in these cases of Kwashiorkor as revealed by liver puncture studies were principally: 1) Fatty change of the liver cells. 2) Fibrosis of the portal tracts.

Both of these features vary from case to case, depending not only on the duration and severity of the illness, but also on early and effective treatment. The latter may restore the morphology of the liver to a nearly normal picture. The fatty change in the liver is the essential lesion present and it seems to determine the clinical course and fate of the condition. It can be explained by the marked hypoproteinemia and hypo-albuminemia which these cases invariably showed.[1]

In the past, this fatty infiltration was looked upon as a terminal phenomenon of little importance. Gillman and Gillman[2,3,4] (1945) were the first to emphasize the fundamental importance of this liver lesion. Again, Waterlow[5] (1948), in his report on the disease in the British West Indies, was so impressed by its significance that he named the disease there, "fatty liver disease".

The second important lesion noticed in these cases is portal fibrosis. This and its relation to liver cirrhosis need a more detailed discussion. Waterlow[5] (1948) presented evidence that "fatty liver disease" may be the precursor of portal cirrhosis developing in childhood. Many authors have suggested that liver cirrhosis in the tropics is caused by malnutrition. Himsworth and Glynn[6] (1944), stated that tropical cirrhosis of the liver may be a "trophopathic" lesion analogous to post-necrotic scarring in rats fed on a diet deficient in sulphur containing amino acids. But even if we agree that cirrhosis in the tropics was caused by dietetic factors, it is probably not the sequel to portal fibrosis of infancy and childhood. In rats, a period of about three months is necessary before cirrhosis of the liver is produced on top of fatty liver (Lillie *et al.* 1942).[7] This period is equivalent to not less than five years in the life of man. (Waterlow).[5] Therefore it is unlikely that a cirrhotic change would occur in the livers of these children within a period of months or even one year.

The portal fibrosis seen in the cases investigated cannot be regarded as "cirrhosis" because nodular hyperplasia and regeneration were not seen. These are important criteria for the correct pathological diagnosis of liver cirrhosis which cannot be ignored. It

seems that for this to take place, the irritant should be continuous or repeated over a much longer period of time i. e., years—as in the case of cirrhosis developing on the top of fatty livers of diabetics and alcoholics. In the present cases, however, the possibility of its occurrence in later years cannot be excluded and it would be of value to repeat the liver punctures in cases where the portal fibrosis was evident some years later.

SUMMARY AND CONCLUSIONS

1. Thirty cases of Kwashiorkor among Egyptian children were investigated with an aim to studying their fate, the effect of treatment on them, and the hepatic changes in this disease.
2. For this purpose one hundred liver punctures were performed and these were studied histopathologically. The punctures were usually performed on admission, at subsidence of edema and during convalescence.
3. It is concluded that the essential pathological finding in these cases is fatty infiltration of the liver cells with or without some degree of portal fibrosis.
4. The fibrosis is marked in some cases, but there is no accompanying nodular hyperplasia of the liver parenchyma and therefore, the authors feel that a diagnosis of cirrhosis is, at the present state of knowledge, not justifiable.
5. The effect of the treatment on the hepatic lesions is mentioned.

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Pinworms — A Ten-Year Study*

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Every physician sees, from time to time, a baffling case which follows no apparent diagnostic pattern. The symptoms may simulate a cerebral lesion, a toxic synovitis, asthma, transient amaurosis, etc., and the etiology and nature of the illness may be obscure. These patients do not respond to standard treatment. In not a few of these cases, an intensive search often reveals a parasitic infestation to be the underlying cause. With patience and careful search the lowly pinworm is often found.

Like syphilis, parasitic infestations can simulate almost any disease and may affect any system of the body, including the central nervous system, the eye, the vascular, the skin, the gastro-intestinal and the genito-urinary system.

DIAGNOSIS

The presence of the pinworm or its ova is the basis for positive diagnosis of enterobiasis. Occasionally a worm may be evacuated following an enema or it may be seen crawling out the anus or vagina. The adult female worm is approximately one-quarter of an inch long, thin as a thread, white, and motile. If a sufficiently accurate description of the worm can be provided by the parent of the patient and if the usual symptoms of infestation are present, a definite diagnosis of enterobiasis can be made.

Generally, however, a meticulous search for ova deposited in the perianal region should be made with either the N. I. H. (National Institute of Health) swab or the now popular modification of the anal swab technique. Ordinary cellulose adhesive tape, three inches long, is looped over the end of a tongue depressor with the adhesive surface outward. After this surface has been pressed against both sides of the perianal area, the tape is transferred to a miscroscope slide, with the adhesive surface against the glass, and is examined under low-power objective. A drop of toluene placed on the slide before the cellulose adhesive tape is applied will dissolve extraneous matter, permitting easier identification of the pinworm ova.

*Originally presented, at the Hartford Hospital Amphitheatre before the Pediatric and Neurological Services.

Fecal examination for ova is an unreliable diagnostic method, because the female worm ordinarily does not lay eggs in the colon. Eggs are present in the feces in not more than five per cent of infected persons.

On innumerable occasions I have admitted children with pinworms to the hospital with infestations so great that the adult oxyurids were found on the perineum or vulva. Paradoxically, in some of these cases, the anal swabs would be consistently negative. Investigation of this problem revealed that occasionally the swabs are taken after the anal region has been covered with vaseline for temperature taking, the nurse may have cleansed the anal area before taking the swab, or the swab may have been incorrectly obtained or interpreted by the laboratory technician.

Despite the high degree of diagnostic accuracy possessed by the anal swab method, difficulty is still encountered due to the periodicity of infection. Inconsistent levels of infection related to the life cycle of the parasite prevent consistently positive results. The infection reaches a peak three to five weeks after it is acquired, subsides to subclinical levels, then builds up again. Thus, diagnostic tests must be repeated on successive days to evaluate the presence and severity of infection, best obtained at 6 a.m. and at midnight.

NEUROLOGICAL MANIFESTATIONS OF PINWORMS

During the past ten years a number of children with neurological symptoms suggesting brain tumors, epilepsy, chorea, diffuse encephalopathy, and other diseases were examined and concurrent infestation with the pinworm was noted. In many of these cases, the electroencephalogram(EEG) seemed to corroborate the presence of an organic lesion. However, following treatment for oxyurias, the EEG frequently reverted to normal. Some examples follow:

Case 1: (B. B.) A six-year-old lad was hospitalized because of awkwardness in running, skipping and standing up. Other symptoms included pain over both temples, squinting, nocturnal complaints as if light were bothering him. For three months he demonstrated weakness of the left arm and leg.

Pertinent findings were irritability, unwillingness to cooperate, questionable left Babinski sign, difficulty in tandem walking and hopping on the left foot. The electroencephalographer reported an excess of slow wave in the left hemisphere, especially in the left parietal region. The records was considered consistent with encephalopathy in the left posterior parietal area.

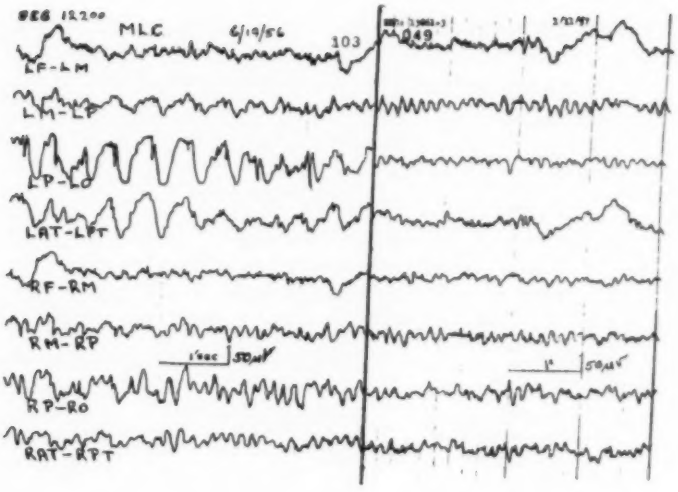
Pneumoencephalogram was negative. The child was discharged on the fourth day of hospitalization unimproved with a possible diagnosis of toxic encephalopathy. The left sided weakness gradually improved.

Six months later he returned to the office. He was irritable and nervous, cried easily, had a short attention span, exhibited peculiar mannerisms (such as picking his nose, frequently adjusting his pants, scratching himself, making wierd unpleasant noises while eating and sleeping) and he had a fleeting erythema about his face. Oxyurids were found in the rectum. Piperazine therapy was instituted. The parasitic infection cleared with simultaneous disappearance of his neurological symptoms. A repeat EEG was too slow for age but showed no focal changes.

Case 2: (T. B.) this two and one-half-year-old child was admitted to the Mt. Sinai Hospital (Hartford) because of afebrile convulsions. Several days prior to admission pinworms were found crawling over her perineum and in her vulva. A pretreatment EEG was considered moderately abnormal because of an excss of low activity somewhat more prominent in right sided leads. Piperazine therapy was then started; no further seizures followed. Three weeks later a post-treatment EEG revealed a moderate but definite improvement. Two years later, non-febrile convulsions and hives recurred accompanying a reinfestation with oxyurias. Child has been well since and has been doing excellent work at school.

Case 3: (M. L. C.) This nine-year-old girl was seen because of convulsions, syncope, and night terrors. There was clinical evidence of oxyuriasis. The first EEG was abnormal and showed slow wave spike discharges in the occipital areas, more on the left. The patient was treated with piperazine for fifteen days. A second EEG, ten weeks later, showed clearing of the occipital dysrhythmia leaving a left temporal sharp wave discharge. The patient remained clinically will over the next months and a final EEG was reported as follows: "Impression: This record is definitely improved over either of the earlier ones. She no longer has an occipital dysrhythmia and there is minimal temporal lobe sharp wave activity." To date the child has been asymptomatic (See figure I.) She continues to show a basic alpha rhythm that is too slow for her age but even this is improving.

Case 4: Dr. Ruth Fox[1] observed an eight-year-old girl with frequent Jacksonian seizures. The consulting neurosurgeon felt that there might be some localized cerebral lesion. Before neurological



EEG of a 9-year-old girl, infested with oxyurias, showing slow wave-spike discharges in the left occipital area (LO)

Recording on the same child showing absence of the occipital dysrhythmia following anthelminthic therapy. (Normal pattern).

FIGURE 1

studies could be made, she passd a large ball of pinworms. Following this she was treated for pinworms with a complete disappearance of all neurological symptoms. Dr. Fox also mentioned a case where transient blindness completely disappeared after pinworm therapy.

EYE MANIFESTATIONS

Clinicians have become aware in recent years that allergy play a significant role in the mechanism of a number of diseases of the eye. Since embryologically, the eye represents widely divergent tissues, it is also subject to widely divergent types of allergy. The avenues of entry of allergens are also multiple, thus allowing diversified types of allergens to act. The action may be direct by contact on the lids and conjunctiva, or internal through the blood stream and other fluid media. Blinking may be due to toxic or allergenic irritation of the facial nerve or its nucleus. In two girls keratoconjunctivitis improved strinkingly after intestinal parasites (oxyurias and tapeworm) had been removed.[2]

Ciliary spasm may be of allergic origin. Feinberg[3] has seen at least one instance of unilateral ciliary spasm, without inflammation, in which an allergy to wheat was demonstrated by repeated elimination and addition. Ciliary spasms can produce temporary myopia. In migraine, which is often of allergic origin, transient diplopia and nystagmus occur not infrequently. It is my belief that dust laden with oxyurias ova may often trigger an attack.

Eye changes may also be explained on a toxic or vascular basis. Spasm of the retinal blood vessels causes diminished blood flow, resulting in edema or small hemorrhages. This may cause scotomata, temporary blindness, and the other evidences of disturbed vision.

The following cases are illustrative of a relationship between oxyurias and ocular symptoms:

Case 5: (S. P.) A six-month-old infant developed spasms nutans, and shortly thereafter nystagmus. There was heavy sibling infestations with oxyurids. Pinworms were found on the patient's perineum. All eye symptoms decreased rapidly after anti-oxyurid therapy.

Case 6: (P. V.) A six-year-old child complained of photophobia, especially at night, plus intermittent poor vision and headaches. Hippus (spasmatic pupillary contractions) was also present. Symptoms coincided with pinworm flareups and disappeared following therapy.

Case 7: (G. D.) A two-year-old child manifested strabismus (convergens) which became worse when he felt "nasty". This always coincided with the passage of pinworms.

Case 8: (A. R.) A two and one-half-year-old child had stumbled frequently for about six weeks. He suddenly passed a large number of oxyurids, was therefore treated with piperazine. Thereafter, he showed improvement in his gait.

Case 9: (L. M.) a four-year-old complained of blinking, eye pain, and photophobia of several weeks duration. Complete disappearance of ocular manifestations occurred after piperazine therapy.

Case 10: (D. E.) A three-year-old child suffered with half-hour bouts of amblyopia several times daily. His eye ached intermittently for about one year. Clinical evidence of pinworms was found. Strabismus and photophobia (especially at night) were present. Siblings were infested with oxyurias. Piperazine therapy was instituted empirically and ocular symptoms cleared.

Case 11: (F. E.) A six-year-old lad to whom things did not look clear especially when he was tired, said that he had to move his eyes upwards ("juggled his eyes") to see sharply during rainy weather. He ate mud and cat food. Finally he passed oxyurids. His eye symptoms disappeared after anthelminthic therapy.

BEHAVIOR PROBLEMS

In a communication from Basel, August 31, 1954, Professor Dr. Robert Bing[4] wrote: "More than half a century ago, Eichhorst, describing the symptomatology of oxyurias, stated that the neurological manifestations consist of headache, dizziness, pupillary asymmetry, eclampsia, chorea, paralysis, pruritis nasi and ani." In a later communication dated April 20, 1955, Professor Bing wrote that trismus or teethgrinding, commonly seen in oxyurias infestations, is considered as produced by trigeminal irritation. Nervous symptoms are frequently noted in infected persons if there is sufficient erosion of the intestinal mucosa to expose sympathetic nerves. Insomnia is common, and even epileptiform symptoms may develop.[5]

Non-specific, undiagnosed irritable behavior in children and in young adults may be due to infestation with a parasite causing allergic or toxic involvement of the central nervous system. In such situations, either the gross presence of the parasite or its laboratory recognition should warrant a trial of anthelminthic treatment.

Observing many children with behavior problems and emotional difficulties in whom pinworms were present stimulated my interest in this problem. Not a few frantic mothers have come to me, upset because of annoying behavior problems in their children. They wanted their "so-called" problem children referred to psychiatrists or to Mental Health Clinics. Prevailing upon them first to let me exclude organic disease, I then sought and found pinworm infestations in many of these children. After deworming, their mothers sheepishly admitted that their children no longer needed psychotherapy.

These children present a definite clinical entity. When they come into the office for the first time, they are terrified, exceedingly apprehensive, irritable, itchy, stamp their feet and squirm through the examination. Many of them have rings around their eyes and a papular peri-anal or gluteal dermititis. As these children grow older, untreated or reinfected, they become whiny, moody, unruly, difficult to live with. Nothing pleases them and they do not know what to do with themselves, making life miserable for their broth-

ers, sisters, and parents. They tease and fight, are impulsive, impudent, and aggressive. As one mother put it, "He is as if possessed of the Devil." They have a short attention span and concentrate poorly at play and at school.

The view that disturbances of behavior may be etiologically related to an allergic process is favored by a large number of allergists and psychiatrists. The Bakwins[6] mention work done by Stevenson who reviewed the subject of allergy in the nervous system and concluded that allergic manifestations in the central nervous system may be produced by ingestion of food, inhalation of pollen, injection of serum or vaccination against bacterial or virus diseases or as

complications of various diseases. To these, I would like to add parasitic sensitivity, as another etiologic factor. In 1922, Shannon[7] pointed out that allergic children were often restless, irritable, unruly, peevish, out-of-sorts, high strung, and difficult to manage. He concluded that many of these symptoms result from irritation of the nervous system because of anaphylactic reactions to food proteins to which the patient is sensitized. Rowe[8] and others have stressed changes in personality and behavior in allergic children. Randolph[9] emphasizes the relations of chronic food allergy to disturbances of behavior. Removal of the offending foods from the diet, or ridding the infested children of their parasites results in marked improvement in their behavior.

HEADACHES

Headaches are a frequent problem in Pediatric diagnosis, often resulting from allergic or hypersensitivity mechanisms. Dewar[10] quotes Kennedy who visualized edema of the skin translated to the intracranial cavity which gives rise to painful areas of edema in the meninges. In my series of over two thousand oxyurias-infested children, the incidence of headaches was 60.5%. A common experience has been that even with associated sinus or upper respiratory infections, concommitant pinworm therapy produces more rapid disappearance of the headaches.

ELECTROENCEPHALOGRAMS

A significant contribution in neuroallergy was the observation of Dees and Lowenbach[11] that abnormal encephalograms are a common finding in many allergic children. They found that there are children with convulsions and allergy whose electroencephalograms do not show the accepted spike and wave or fast wave pattern thought to be characteristic of idiopathic convulsive disorders but rather an entirely different pattern, occipital dysrhythmia. Such children, having failed ot respond satisfactorily to anticonvulsant drugs alone, are often further benefited by control of their allergic disorder. The similarity between the electroencephalograms of allergic children with or without convulsions suggests that allergic reactions may affect the central nervous system in certain susceptible individuals, and that clinical convulsions may be the expression of an exceeded threshold in such patients.

Recently "bilateral occipital slow activity" has been associated with epileptogenic processes,[12] behavior disorders, intrinsic brain disturbances,[13] maturation defects,[14] psychopathy, and with allergy

of the central nervous system,[15] and ocular disorders. Seventy-five per cent of Cohn and Nardini's patients with bi-occipital slow activity showed varying intensities of aggressive clinical behavior. The individuals between the ages of 6½ and 17 years were observed to have difficulty in school adjustments, play and other social function. The primary difficulties consisted of unruliness, hyperactive play, strong sense of acquisitiveness, failure to be considerate of their associates, and inability to respond appropriately to their supervisors.

In the present series of 150 proven cases of children with oxyurias infection 63 of their electroencephalograms (42%) showed occipital dysrhythmias. Repeat tracings taken about one to two months following successful anthelminthic therapy revealed disappearance or diminution of the occipital dysrhythmias in 30 cases (48%).

RESPIRATORY AND ALLERGIC SYMPTOMS

Allergists have long been aware that in a certain segment of their practice they are unable to determine the etiology of a patient's wheeze. Veterinarians tell us that a very common cause of wheezing in pups is worms. In some of my "asthmatic" patients there was a distinct correlation between the presence of oxyurias and asthmatic attacks. A pleasant surprise came when some of the asthmatic attacks abruptly ceased after pinworm therapy.

A peculiar brassy, staccato, non-productive cough is frequently seen which is due not to a post-nasal drip but rather to the ascension of oxyurids in the alimentary canal, whence they wander into the upper-respiratory tract. Lingering "colds" are often shortened by concomitant anthelminthic therapy.

BLEEDING TENDENCIES

It is an accepted fact that pinworm infestation is the most common cause of rectal bleeding in chi[illegible]n. This is often due to submucosal ulceration in the intestines or rectum by the adult parasites.

During the height of parasitic infestations there appears to be a correlation between the infestation and an increased tendency to bleed from other areas of the body such as the nose, the gums, and the skin after minor trauma. Should the height of the infestation coincide with menstruation, it may prolong or increase the menstrual flow. Hematuria is a very common occurrence. One urologist (Dr. Harold Lear) who has become interested in this subject has actually found oxyurias to be the etiologic factor in 50% of the cases

of hematuria in young girls. He advises omitting unnecessary urological procedures if hematuria disappears following eradication of the pinworms.

I have recently seen two cases of Henochs-Schonlein purpura which were triggered by the presence of hords of pinworms. Platelet counts, coagulation time and prothrombin time have been normal. In some, there has been a slight prolongation of bleeding time. It is possible that a similarity exists between parasitic-induced bleeding and the hemorrhagic tendency induced by the bite of leeches and venomous snakes. Research is indicated to help explain this phenomena.

COLIC

The literature is rich in the cause of colic in infancy. Rarely, however, does one see mention of oxyurias as an etiologic factor. Particular attention was paid to the newborn in fifty families infested with the oxyurias. Blood counts performed during the neonatal period revealed eosinophilia (5% or higher) in sixty-eight per cent of these newborns. The oxyurias can be found during the second month of neonatal life. Nearly all of these newborns exhibit a severe, intermittent type of colic. Some of them showed a "raspy" type of breathing, others a transient blotchy erythematous eruption, and many a fine perianal papular eruption. Treating these babies early is effective in eliminating colic. Van Thiel[16] has found the eggs of oxyuris in mesenteric lymph nodes.

LIMP

It has been my policy to look for parasitic infestations in cases of "toxic synovitis" or limp which do not respond to the usual orthopedic treatment. Studying a number of children in whom other causes of a limp had been eliminated, I found a considerable percentage of them to be infested with parasites. Several of these cases had been treated with traction with little or no response. Anthelminthic therapy or the spontaneous passage of pinworms cleared up many of these cases.

Several mechanisms present themselves as possible explanation of this phenomenon in children. Irritation of the perianal and perineal skin dermatomes causes reflex spasm of the sphincters and the musculature of the rectum (levator slings) and of the gluteal muscles. Pinworms often lead to constipation. A fecal impaction in the distended colon may exert pressure directly onto the ileo-psoas muscle resulting in irritation or spasm of the thigh thus producing

a protective or pseudo-limp. Furthermore, neurologically, a toxic neuritis may produce a limp. The neuritis may be due to edema of the myelin sheath.

PICA

Pica should be considered abnormal after eighteen months of age. Retarded children develop this condition more frequently than normal children. Many children with pica ingest dirt which contains ova and therefore ova and parasites are often found in their stools.[17] Following are listed objects that some of my patients with pica have eaten: burnt matches, cigarette butts, cigar ashes, blanket fuzz, hair, crayons, putty, chalk, mud, cat food, garbage, juniper berries, seedpods, paper, shoes, and aspirin. Apparently many of them consider burnt match sticks a delicacy. As one mother recently told me—"Billy must have the worms again. He is back on his 'Goat Diet'."

Interestingly enough, ten cases of proven lead poisoning in children had a concomitant infestation with oxyurias. Apparently, pinworm infestation in some children causes pica, which in turn may lead to lead poisoning. Having cured a child once of lead poisoning does not always end the problem, for further reinfestation with enterobiasis may lead again to recurrent plumbism. Hence, the need for keeping these children dewormed is obvious.

TRICHOTILLOMANIA

I have observed trichotillomania (an uncontrollable impulse to pluck out one's hair) in thirty-one patients with oxyurias. Dramatic relief is obtained either during or upon completion of anthelminthic therapy. The following case is illustrative:

Case 12: (B.J.) This seven-year-old child was bright mentally, and took a normal interest in his environment. Drugs prescribed to "quiet the nerves" and punishment or threats directed against the continuance of the practice of pulling out his hair had all proved unavailing. His appetite was capricious. Examination of the perineum revealed pinworms. With anthelminthic therapy, "hair pulling" ceased. Anemia and appetite improved.

SKIN

Pinworm infestation is not a disease limited to children. It is carried through adolescence into adulthood. According to Craig and Faust[18] in 25% of the cases of oxyurias infestation the parasite migrates up the gastro-intestinal tract and the gravid female oxyurid may deposit ova outside the nasopharynx. This may result in the

formation of small showers of fine papules in the perinasal and perioral areas. The resulting pruritis causes the host to scratch. This often causes the lesions to become secondarily infected with staphylococcic organisms. Hence one frequently finds facial impetiginous lesions in children or adults heavily infested with oxyurias. Styes apparently are similarly formed. In the early teens we find facial lesions, triggered by the oxyurids, as a precursor to acne.

In 75% of the cases the female oxyurid deposits her ova on the perineum. The resulting pruritis ani leads to scratching. Pyodermic lesions soon appear and many of these turn into abscesses. In one five-year-old girl (G. A.) daily at 5 p.m. for a few weeks "shower of small papules" would appear over her perineum and groin. These would progressively get worse until 10 p.m. when she would fall asleep. By morning the skin would be clear. This condition cleared after anthelminthic therapy.

ACCIDENTS

Children and adults are more prone to accidents at the height of a pinworm infestation. Apparently their hyperactivity and carelessness interfere with muscular coordination making them more amenable to injury. These children are often hostile, impulsive, drop dishes, are clumsy in their gait, fall off their bicycles easily, bang themselves and cut themselves frequently.

Infested mothers often dent their cars, pass through red lights, burn themselves with their electric irons, rip their stockings, yank their offspring's arms while shopping at the supermarkets, forget to turn off their ovens, etc. Seventy-five per cent of all fires are caused by human carelessness and forgetfulness which themselves may be the manifestations of ill health, irritability, or distractability.

Reviewing psychological and psychiatric factors of highway accidents, McFarland[20] concludes that "a man drives as he lives." It is the driver's personality rather than his capacity, age or skill that plays the main role in accident causation. Involved in most of the repetitive accidents are infantile, immature or conflict-ridden and rebellious or exhibitionistic individuals.

WEATHER

A correlation exists between exacerbations of oxyurias infestation and humid weather. Moisture and temperature play an important role in the development and survival of pinworm eggs. Survival is best under cool, moist conditions but the eggs can also de-

velop in six hours in a high humidity and warm temperature. Excessive humidity in the atmosphere causes egress of the pinworm. On humid days, especially when the barometer drops, I can foretell that new cases of pinworms or flare-ups of old dormant ones will appear.

TREATMENT

Experienced physicians treat entire families when one or more are infected and repeat a course of treatment or prolong it if reinfection occurs with a view of eliminating simultaneously all sources of pinworm infection in the household.

Many drugs by mouth and by enema have been used singly and in combination for the treatment of pinworms. Several old-world remedies are:

CANADA	Poplar bark-ground infusion: Diphenan (Parabenzylphenyl carbonate)
GERMANY	Wörmerkraut
GREECE	Asafetida in bags around the neck
GYPSY REMEDY	Baking soda enemas
ITALY	Spirits of Turpentine—5 drops in warm water for 4 days; Nicotine obtained from the inside of a smoked tobacco pipe, used as snuff twice daily for 4 days
PUERTO RICO	Garlic enemas used by the School of Tropical Medicine in Puerto Rico; Jagua—an herb (under study)
RUSSIA	Olive oil enemas daily for 4 days
SWITZERLAND	Aloxyne=aluminum—8hydroxyquinolin sulfate

In the United States the following have been employed:

1. Dr. True's Elixir (made from senna leaves and aloin)
2. Boykin's worm medicine (Washington, D. C.)
3. Caraway seeds=1 teaspoonful served with rasberry jam monthly, administered during the full moon
4. Sulfur and molasses (Spring tonic and vermifuge)
5. Cathartics: Casafru, licoric powder, senna preparations, Castor oil
6. Quassia chips (enemas) 15% effective
7. Hexylresorcinol enemas (toxic)
8. Garlic (Allisantin—deodorized garlic tablets)
9. Pyribenzamine (triplennamine hydrochloride)
10. Gentian Violet: Tablets, suspension, supprettes
11. Oxytetracycline—too expensive, too irritating
12. Tetrachlorethylene
13. Syrup of Perin—piperazine calcium edathamil
14. Antepar, Pipizan—piperazine calcium edathamil
15. Delvex—dithiazanine iodide
16. Vanquin pamoate—pyrvinium pamoate—Povan

The so-called 100% single dose cures are disappointing!

Piperazine, dosage by body weight for 10-14 days, is the most frequently used anthelminthic, because it is the best-tolerated, even though it is less efficient than some of the harsher drugs (i.e., gentian violet). The disposable phosphate enema (Fleet) has been helpful in the treatment of fecal impaction and chronic constipation,

conditions commonly accompanying parasitic infestations. There is still a crying need for a well-tolerated and yet more efficient anthelminthic than is available to date. The treatment of the secondary anemia which often accompanies pinworm infestation usually responds to appropriate, well-tolerated hematinics.

The following Public Health measures (Ten Commandments) have been suggested:

1. Close-fitting underpants should be worn night and day to prevent pinworm eggs from dropping from the host; when removed, bed clothes and bed linen should be well laundered.
2. Daily bathing and each patient should keep his fingernails short and should scrub his hands after bathroom use and before each meal.
3. Separate wash cloths and towels for face and body would safeguard autoinfection.
4. Infested individuals should not share the same bed with non-infected family members.
5. Toothbrushes should not be exposed to bathroom dust.
6. Vacuum cleaning should be performed daily to remove some of the eggs with the house dirt.
7. Superheat the home to 95°F. or higher for a whole day as frequently as practicable (warm air destroys eggs), and keep all rooms, especially the bedroom, well-aired.
8. It is advisable to scrub toilet seats daily.
9. Strict personal cleanliness and keeping the children's fingers out of their mouths would prevent reinfections.
10. An educational program designed to reach the public, especially parents, to teach them how infection is spread.

DISCUSSION

It is clear from the foregoing that almost the entire spectrum of pediatric symptoms has been found to be closely related to oxyurias infestation, with these symptoms largely reversible following adequate therapy. The question of *controls* always arises, but in such a study there no such thing as a "normal," for man is constantly infested with the pinworm or other parasites. Of worldwide distribution, the pinworm affects at least one-third of all children.[21] This figure is far too low. In Holland, the incidence of oxyurias infestation has been reported to be 100%!

It is likely that the effect of pinworms on the human organism is mediated via several different mechanisms. Local irritation with itching is obvious. As this factor persists, generalized irritability, restlessness, fatigue and abnormal behavior frequently supervene. It is probable that the pinworm also attacks the body systemically, through a neurotoxin, an allergen, or some abnormal biochemical substance.

The effect of this pinworm onslaught on the human organism, of course, varies greatly, depending upon many factors such as extent

and duration of infestation, host resistance, host sensitivity, as well as previous sensitization. It is my belief that repeated attacks of parasitic infestations may exert a cumulative effect in certain individuals, especially on the nervous system. When the degree of stress becomes sufficient the various symptoms discussed above may appear singly or in a great variety of combinations.

Of particular interest to the author has been the neurological problems related to oxyurias and the close association to abnormal electroencephalography which has been observed. In some children with convulsive disorders, or merely with occipital slow wave abnormalities, complete reversal has been observed following pinworm therapy. Behavior problems, too, have shown similar response. It is clear that in many of these cases, factors other than parasitic infestation alone are of importance. However, when a basic neuroliogical abnormality is already present, oxyuric infection may produce unusual and correctible complications.

In tropical countries it is recognized that parasitism may be the cause of central nervous system disease and of toxic psychotic reactions. In Malibar, South Indian, quoting Dr. Chaco:[22] "I don't treat anyone(from the Bishop to the sweeper, till I get rid of the worms and see how many symptoms are left." In this country (especially the northern part), because there has been a rarity of infestations with tropical parasites, our endemic types have been ignored. In view of the reactions produced by tropical parasites, there is need for investigation of our indigenous parasites to correlate their role in a variety of some of our common ailments.

CONCLUSIONS

Pinworm infestation, an extremely widespread entity, may produce a great variety of symptoms and signs. An awareness of this relationship will frequently allow simple treatment to eradicate or control otherwise puzzling clinical phenomena. Keep watch for the lowly pinworm. It should not be underestimated!

The following clinical manifestations have been observed and cleared up or improved under anthelminthic therapy:

SPECIALTY	*CLINICAL MANIFESTATIONS*
ALLERGY	Asthma, generalized urticaria
DERMATOLOGY	Skin lesions: Papular dermatitis, erythema, hives
GASTRO ENTEROLOGY	Pyrosis, singultus, gastro enteritis, ulcerative enterocolitis, sub-mucosal ulcerations
GYNECOLOGY	Vaginitis, salpingitis, sterility, oxyuris granuloma (meso-salpinx, subserosa)

HEMATOLOGY	Epistaxis, purpura
NEUROLOGY	Migraine, pseudo-brain tumor, epilepsy, toxic encephalopathy, chorea
OPHTHALMOLOGY	Blinking, photophobia, transient blindness, spasms nutans, choked discs, retinal hemorrhage
ORTHOPEDICS	Limp (toxic synovitis)
PEDIATRICS	Dermatitis, anorexia, constipation, behavior problems, pica, onanism, etc.
PROCTOLOGY	Pruritis ani, rectal polyps, tabs or subcutaneous tumors, rectal bleeding, rectal fissures, impacted feces
PSYCHIATRY	Behavior problems, trichotillomania, difficult child, disturbed child, neurosis, neurasthenia, juvenile delinquency, nymphomania, satyriasis, nagging wives (psychoses?)
SURGERY	Appendicitis, epigastric pain, mesenteric adenitis, intestinal pseudo-occlusion, abscessed buttocks
UROLOGY	Hematuria, enuresis, cystitis.

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Activities of the Poison Control Center . . .

ASPIRIN POISONING (A Fatal Case Report)

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THIS patient, a one-year-old negro male child, was presumably in good health until 7 p.m., June 27, 1961, when he vomited four or five times following his evening meal. He also appeared lethargic and was put to bed by his 17-year old mother. He also vomited several times during the night. On the following day, June 28, at 8 a.m., he was found to be morbidly tachypneic and hyperpneic. He was taken to the Beth El Hospital Emergency Room where the child was noted to be stuporous and hyperventilating. The respirations were 44 and the pulse rate 140. No signs of acute infection were manifest.

In view of the findings on admission, a tentative diagnosis of salicylate poisoning was made. Though questioned repeatedly about the possibility of salicylate ingestion, the mother denied it vigorously and insisted that the child was not given any drug nor could he have accidentally swallowed any. Blood was immediately drawn for a chemical analysis and an intravenous cut-down was performed. The laboratory data revealed the following: CO_2 was 25 volume %, Chlorides 101 mEq/1., Cl. 225 mg/100 ml, blood pH 7.35, blood salicylate level 69 mgm per 100 ml. The urine pH was 5.3 and there was a trace of albumin and glucose. It also contained 4-6 red blood cells and 2-3 white blood cells per high powerfield. The hemoglobin was 7.8 grams; hematocrit 33. The white blood count was elevated to 30,700 with 70% polymorphonuclears. The smear was hypochromic and microcytic. The chest x-ray did not reveal any pathological findings.

On admission to Beth El Hospital the infant voided 30 cc of urine and did not void again during his stay at this hospital (16 hours). He was started immediately on intravenous therapy. The intravenous fluid therapy was calculated on the basis of 1800 cc per meter sq. Initial fluid therapy consisted of glucose and isotonic saline. It was felt that after patient had a good urinary void multi-electrolyte fluid would be administered. During his stay at this

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hospital he received a total of 360 cc of glucose and isotonic saline. Blood was crossmatched so that it could be administered in view of the low hemoglobin and a hematocrit of 33. It was felt that if the infant did not respond to the usual regimen or if a renal shutdown were impending he should be transferred to another institution which had an artificial kidney available for hemodialysis. At 5 p.m., or 8 hours after admission, the CO_2 determination was 50 volumes per cent and the chlorides remained the same, 101 mEq/liter. The temperature rose to 104°F.

It was now decided to transfer the infant to the Pediatric Service of the Jewish Hospital of Brooklyn which has an artificial kidney unit available for use. Because mother could not be located, transfer was delayed until 1:05 the following morning, June 29th.

On admission to the Jewish Hospital, patient appeared extremely hyperpneic with Kussmaul breathing and occasional nodding of the head to the right side. He appeared in very poor condition. He was unresponsive even to severe pain stimuli. Eyes racted to light and accommodation and the fundi were normal but the conjunctivi were pale. The fontanelles were slightly depressed. The chest was clear and there were no rashes or petechiae observed anywhere on the body surfaces. The abdomen was soft and the liver and spleen were not enlarged. He appeared to be fairly hydrated though the mucous membranes were dry. There were no deep tendon or superficial reflexes obtainable. On opening the eyelids, a nystagmus was observed. The first chemical blood analysis on admission showed:

CO_2 content of	3.0 mEq/l
Sodium	149 mEq/l
Potassium	5.9 mEq/l
Chlorides	113 mEq/l
Urea	67 mg %

Prothrombin time was 22.6 seconds and the control was 11.5. The blood salicylate level was 41 mg %.

Patient was catheterized and had a good urinary output. He was given the following mixture intravenously: 400 cc of 5% glucose and water; 40 cc saline; 92 cc M/6 lactate.

A second blood determination done at 3 a.m. on the day of admission, June 29, showed a CO_2 content of 4.7 mEq/l and a blood salicylate level of 34 mg %, and a 3rd determination done three hours following the 2nd, or at 6:30 am., showed a CO_2 content of 10.4 mEq/l and a salicylate level of 37.0 mg%. In spite of therapy, child did poorly and expired at 7 a.m., 6 hours following admission to the Jewish Hospital of Brooklyn, and within 41 hours following the ingestion.

The clinical diagnosis was Salicylate Poisoning (accidental). The necropsy findings were as follows:

Gross Description: The body is that of a well-developed, well-nourished male child measuring 172 cms. There is a cut-down in the right medical malleolar area and several needle punctures in both inguinal regions and lumbar regions. The head is symmetrical, covered with hair. The pupils are equal, each measuring 0.3 cm. in diameter and the corneas are cloudy. There are four upper and lower front teeth. There is no rigor mortis. On opening, both pleural cavities as well as the peritoneal cavity are free from fluid.

Thymus: The thymus weighs 11 grams. The external surface is pale pink. On section, no remarkable gross features of note.

Thyroid: The thyroid gland weighs 3 grams. There are no remarkable gross features of note.

Heart: The heart weighs 28 grams. The parietal and visceral pericardium is not remarkable. Several petechial hemorrhages are noted in the epicardium. The superior and inferior vena cava are of average caliber and located in their usual sites. The right auricle is not remarkable. The endocardium is reddish pink. The tricuspid valve measures 5 cm. in circumference. The cusps are thin and delicate. The right ventricle measures 0.1 cm. in thickness. The endocardium is smooth. The pulmonary artery is of average caliber and the pulmonary valve measures 3.1 cm. in circumference. The cusps are not remarkable. The left auricle is not enlarged. The endocardium is smooth and reddish brown in color. The mitral valve measures 2.8 cm. and shows no remarkable gross features of note. The left ventricle measures 0.4 cm. in thickness. The aortic valve measures 2.8 cm. in circumference. The cusps are thin and delicate. The aorta and main branches show no remarkable gross features of note.

Lungs: The lungs weigh 135 grams. The external surfaces are reddish pink. There are several petechial hemorrhages in the visceral pleura. On opening the trachea, the inner surface is lined by a pale pink mucosa. A small amount of mucoid material is contained in the lumen of the trachea and bronchi. On section of the lungs, the cut surfaces are pale pink and a small amount of blood exudes on pressure.

Liver: Weighs 280 grams. The external surface is not remarkable. On section the cut surface is pale brown with moderate congestion.

Pancreas: Weighs 15 grams and shows no gross features of note.

Spleen: The spleen weighs 29 grams. On section, the cut surface shows prominent follicles. The capsule scrapes with difficulty.

Adrenals: Together weigh 5 grams and the external surfaces are not remarkable. On section, the cortex and medulla are fairly well preserved.

Kidneys: Each kidney weighs 24 grams. Both capsules strip with ease. The external surfaces are pale pink and smooth. Fetal lobulations are noted. On section, the cortex and medulla are fairly well preserved. The pelves and ureters are of average caliber and and are lined by a pale pink mucosa. One or two petechial hemorrhages were noted.

Urinary Bladder: No gross features of note.

Brain: The brain weighs 980 grams. The dura is thick, the arachnoid is thin and delicate. No other remarkable gross features noted.

Pituitary Gland: Normal size, shape and consistency.

Microscopic Description:

Heart:	Congestion
Lungs:	Small focal areas of atelectasis and congestion
Liver:	Congestion
Pancreas:	Not remarkable
Kidneys:	Congestion
Lymph Nodes:	Congestion
Testes:	Congestion
Aorta:	Not remarkable
Thymus:	Congestion
Urinary Bladder:	Congestion
Prostate:	Congestion
Thyroid:	Congestion
Adrenals:	Congestion
Spleen:	Necrosis of some germinal centers. Marked congestion with focal hemorrhages.
G.I. Tract:	Congestion
Skin:	Not remarkable
Bone Marrow:	Congestion
Brain:	Congestion
Anatomical Diagnosis:	1. Petechial hemorrhages: (a) Epicardium. (b) Pleurae. 2. Visceral congestion, generalized, marked. History of salicylate poisoning.

SUMMARY

One-year-old negro male with Salicylate Poisoning: A Public Health Nurse visited the home to obtain additional epidemiological information and to give some guidance to the family on how to avoid such accidents in the future. It was learned that the family was entirely unaware that the infant accidentally ingested some

aspirin, until it was suggested by the physicians in the hospital about 15 hours following the onset of vomiting, or 17 hours following the ingestion.

Mother recalled that on the day of occurrence, June 27, at 4:30 p.m., child's aunt took away an aspirin bottle the child was holding. The bottle contained an unknown number of 5 gram aspirin tablets and was placed on a low table in the bedroom. The child took the bottle and apparently swallowed an unknown number of tablets. After the child's death, the container with the remaining tablets was taken by the Police Department.

The family is in the low socio-economic level, on welfare, and the mother is unmarried. Another sibling is under supervision of a Health Department child health station and is doing well. The mother was very cooperative and gave information freely. The patient was a normal full-term infant of average growth and development, and had not been involved in previous accidents. While in the home, the public health nurse also observed a defective side arm water heater, which was reported immediately to the Bureau of Sanitary Inspections for appropriate action. The accident was judged "preventable" and mother agreed that drugs should not be placed where young infants and children could obtain them with ease. This case is cited because it serves to point out the need for continuously alerting physicians and families on the need for employing the necessary precautionary measures in the handling and storage of drugs.

It may be well to indicate that since the beginning of this year, 775 incidents of aspirin poisoning were reported to the New York City Poison Control Center with one fatality. Accidental poisonings are related to availability and accessability of products. Physicians should instruct patients against self medication, against buying large amounts of a medication, and on the urgent need to keep all drugs away from children who normally put everything in their mouths.

Grateful acknowledgements are expressed to Beth El and to the Jewish Hospital of Brooklyn for making available to us all the pertinent information about this accidental poisoning.

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(*This is the thirteenth of a series of papers by Dr. Jacobziner*)

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